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11ZGERALL EXAMINER

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ART UNIT	PAPER NUMBER
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1812

18

DATE MAILED: 02/22/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4 Nov 1994 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-33 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-33 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1. Applicant's amendments have obviated the objection regarding duplicate claims (¶ 4 of Paper No. 13).

In connection with the objection regarding the absence of SEQ ID NO's in the claims (¶ 3), Applicant is correct that the necessary information was introduced by preliminary amendment. When a substitute Sequence Listing was filed on 10 January 1994, renumbered claim pages were also submitted, although the amendment did not instruct their entry. These were inadvertently marked up as the claims of record, and the preceding amendments were not transferred to the new pages. This clerical error has been corrected: the original claims pages (which, following the insertion of the new Sequence Listing, have been renumbered by the Office) are the claims of record. The duplicate claims pages submitted on 10 January 1994 remain in the application file with the rest of the amendment but are not now entered as a part of the specification.

Insofar as the rejections of record are maintained below, Applicant's arguments filed 4 November 1994 have been fully considered but they are not deemed to be persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claim 21 is objected to for the use of unconventional Markush language. In attempting to adopt the Examiner's suggestion in the last Office action, Applicant's amendment omitted the word "selected". The amended claim is awkward as it recites "a process from the group consisting of". It should be amended to recite "*selected* from the group" so that the intent of its structure will be clear.

3. The specification is objected to under 35 U.S.C. § 112, first paragraph, because the specification as filed does not provide support for the invention as now claimed.

The specification does not provide support for claiming the C-chain of IGF-I, IGF-II, insulin, or "fragments thereof" as specific embodiments of non-naturally occurring prorelaxin C peptides. The sections of the specification which Applicant indicates as providing support for the new claim language discuss manipulations of available expression vectors containing, *e.g.*, pro-IGF's, but in all cases those manipulations ultimately involve the excision of the coding sequences of the non-relaxin prohormone coding sequences. The specification simply does not teach or suggest with even the least particularity that the C-chain of any non-relaxin prohormone (or any fragment thereof) may be used in the instant invention.

4. Claim 33 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth immediately above in the objection to the specification.

5. Claims 1-33 remain rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth at ¶ 5 of Paper No. 13, as the disclosure is enabling only for claims limited to prorelaxins having C chains of "about 8 to 15 amino acids". See M.P.E.P. §§ 706.03(n) and 706.03(z).

It is maintained that the claims read on a greater scope of embodiments than are supported by the disclosure. Applicant considers that the Examiner's reading of the claims to encompass C chains of arbitrary length, including hundreds or thousands of amino acids, is "unsupported conjecture". However, the Examiner is obliged to give the terms employed in the claims their broadest reasonable meaning in light of the specification. In the instant case, the only material restriction which the disclosure places on the C peptides of the invention is that they be "non-naturally occurring". It is therefore believed to be reasonable to consider that Applicant intended to claim prorelaxins comprising *any and every* peptide sequence other than the natural C chain as the portion separating the A and B chain sequences.

Furthermore, at issue is not only the scope of prorelaxins which *are capable* of refolding, but the scope of prorelaxins which can be properly refolded *according to the teachings of the disclosure*, absent undue experimentation on the part of the skilled artisan. That, as Applicant argues, assays are disclosed which permit the artisan to determine whether the refolding of a given prorelaxin has been successful, does not lead to the conclusion that adequate guidance has been provided to direct him to the methods which will be useful to refold any prorelaxin encompassed by the claims. It remains that an indeterminate level of experimentation would be required of the artisan to ascertain *how* to refold any given prorelaxin, thus to practice the invention in the manner disclosed, and it is maintained that for a certain part of the subject matter encompassed by the claims, such experimentation would be of such quantity and character as to be undue. (It is noted that Applicant's comments concerning biological activity anticipate an argument which the Examiner does not find necessary. As the product of refolding and excision of the C peptide will in every case be a mature relaxin, the activity of the product is not questioned.)

For the reasons elaborated in the last Office action, it is maintained that the artisan would *expect* that prorelaxins having extremely long or extremely short C chains would not be capable

of folding *under any conditions* to a form which, upon cleavage, would yield mature relaxin. Furthermore, it remains the Examiner's considered opinion that it would require undue experimentation of the artisan to determine a protocol suitable for folding prorelaxins of substantially different structural character than the "mini-C" protein for which a protocol is provided.

The Examiner's conclusion relies heavily upon the teaching provided in *Applicant's specification* that the redox conditions required for (re)folding are "critical and protein specific" (page 19, lines 24-25). The protein to be refolded in the instant invention is a prorelaxin which will be distinguished from other prorelaxins by its C chain. Even though the final product, following cleavage, is the same mature *relaxin* hormone, a protocol which is suitable for refolding one *prorelaxin* will not necessarily be suitable for another. Moreover, the argument presented in Applicant's reply, that "one of ordinary skill in the art could . . . refer to any number of redox/protein folding-related publications, to identify any number of conditions under which proper refolding of the prorelaxin molecule would occur", is directly at odds with the express teachings of the disclosure.

Certainly there is merit in Applicant's argument, that the exemplification of the refolding of only one prorelaxin using the protocol disclosed should not limit the scope of the claims to that single embodiment, and the Examiner has reconsidered his position with respect to this point. The question which must be addressed is for what scope of prorelaxins does this single example provide sufficient guidance such that the experimentation required to practice the invention not be undue. In reviewing the disclosure, the Examiner can find only the teaching that "[p]referred are C chains having about 8 to 15 amino acids" (page 10, line 30) to link the particularly disclosed embodiments to a scope of subject matter that is not as broad as that encompassed by "a non-naturally occurring C-chain". One skilled in the art would consider that, to a good first approximation, the conditions disclosed for refolding "mini-C" would be appropriate for folding other prorelaxins having C chains of similar length; thus the Examiner considers that claims limited by the recitation of a C chain of "about 8 to 15 amino acids" would reasonably be supported. (It is noted that claims 16-18 and 25-27, which recite particular 13-amino acid sequences, remain broader than the enabling disclosure as they require only that the C chains "comprise" the sequences specified.)

Applicant's arguments relative to the use of Carboxypeptidase B are persuasive, and the rejection is not maintained on this ground.

6. Claims 22 and 33 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 remains rejected as it recites a "formulation buffer" without antecedent basis in the specification. As no guidance as to the meaning of this term is provided therein in the form of definition, discussion, or exemplification, the metes and bounds of the claim cannot be ascertained as they depend upon such meaning.

Claim 33 recites the construction, "comprised of", which was the basis for the rejection under this section of other claims in the previous Office action. It is not clear whether the intended meaning is "comprises" or "consists of", and the claim should be amended to recite one of these alternatives.

7. The following rejections under § 103 are maintained for the reasons set forth at the indicated paragraphs of the last Office action:

Claims 1-8, 21-24, 30-32, and new claim 33, over Hudson (U.S. 5,179,195) in view of Chang (*BBRC*, 1990) and *Enzyme Nomenclature* ("EN", 1984) (¶ 9);

Claims 14 and 15, over Hudson, Chang, and *EN* as applied to claims 1-8, 21-24, and 30-33, and further in view of Stults (*Biomed. Environ. Mass Spectrom.*, 1990) and Dimarchi (*Int. J. Pept. Prot. Res.*, 1982) (¶ 10); and

Claims 9-13, over Hudson, Chang, and *EN* as applied to claims 1-8, 21-24, and 30-33, and further in view of Olson (U.S. 4,518,526) (¶ 11).

Applicant's traverse of all of these rejections is based upon the argument that since "Hudson . . . does not exemplify a process for making relaxin using a single chain polypeptide" (Applicant's emphasis), the reference "does not provide . . . a reasonable basis for expecting that a modified C-chain would yield an operative prorelaxin or relaxin protein". The Examiner does not accept this premise. Exemplification is not prerequisite to enablement, as indeed Applicant argues in traversing the rejection under § 112, first paragraph, discussed above. In this case, Hudson expressly teaches

. . . in a similar manner to insulin, relaxin may be prepared from prorelaxin by oxidizing or otherwise converting the sulfhydryl groups on the A and B peptides of relaxin, prepared as described herein, to form disulfide crosslinks between said

A and B peptides, and then excising the C peptides, for example, by an enzyme-catalyzed hydrolysis specific for the bonds joining the C peptide to the A and B peptides.

(Col. 7, lines 50-57)

5 The reference clearly teaches that (i) relaxin may be readily made from a recombinantly produced, single-chain prorelaxin polypeptide, and that (ii) guidance for the procedures needed to do so may be found in the procedures already known to the art for making insulin from proinsulin. These teachings by themselves are sufficient to establish *prima facie* that the Hudson disclosure is enabling for the production of mature relaxin from a single prorelaxin polypeptide, and Applicant has provided no evidence which calls these teachings into question. The assertion that Hudson provides no "reasonable expectation of success" in the practice of the invention it discloses and claims is therefore not persuasive. As no other aspect of the rejections has been argued, the rejections are maintained.

8. U.S. Patent No. 5,145,962 to Hudson *et al.*, cited as being of interest in the last Office action, is again noted. Like U.S. 5,179,195, relied upon in the § 103 rejection above, it claims subject matter encompassed by some of the instant claims. Neither patent, however, claims *identically* an embodiment which meets the limitations of the instant claims. Claim 4 of each omits to expressly recite a signal or leader peptide, as required by instant claims 23-28, although the patent claims encompass such embodiments.

9. Claims 16-20 and 25-29 remain free of the prior art, although for reasons other than those elaborated in the last Office action. The claims as amended encompass substantially more subject matter than that to which Applicant's unexpected results apply. However, the art provides no motivation to make the particular sequences claimed. All of these claims would be allowable were they amended to recite closed language in reference to the C peptide sequences (*i.e.*, "consisting of" or "having" the recited sequences).

It is believed that all pertinent arguments have been addressed. No claim is allowed.

10. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

5 *A shortened statutory period for response to this final action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this final action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than six months from the date of this final action.*

11. Any inquiry concerning this communication should be directed to David Fitzgerald, who can be reached by any of the following means:

Telephone (703) 308-3934

Fax - Art Unit 1812 (703) 308-0294 ~~note~~ note the new fax number

Internet dfitz@uspto.gov or dfitz@pioneer.uspto.gov


Examiner Fitzgerald is generally available Mondays through Thursdays from 8 a.m. to 5 p.m. (Eastern), and during the same hours on alternate Fridays. If he is not available to take a call, a message may be left on his voicemail. Should attempts to reach him be unsuccessful, his supervisor, Garnette D. Draper, may be reached at (703) 308-4232.

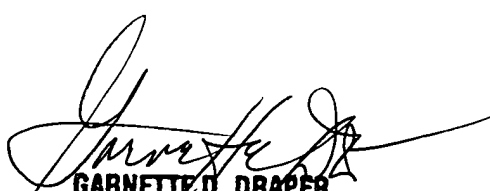
Note that papers of record may be submitted to Group 1800 by fax; refer to 1096 OG 30. Submission of a confirmation copy through the mailroom is **not** required; duplicate submissions are discouraged since entry of two copies of the same paper will tend to confuse the record. Applicant should, however, retain on file the original copy of any formal paper which is submitted by fax.

The Group now maintains 8 fax machines. While papers may be submitted to any of these, the use of the number noted above will facilitate the matching of papers for this Art Unit with the appropriate cases. To expedite the delivery of draft or informal papers, such communications should be clearly marked on the first page as **INFORMAL COMMUNICATION, COURTESY COPY**, or the like. It is also a good idea to call the Examiner when an urgent communication is faxed so that he knows to expect it.

The Examiner checks his e-mail messages at least every morning. Internet e-mail is **NOT** considered to be secure; confidential information should therefore be transmitted only with encryption of the data files. There is at present no procedure which allows for the submission of formal communications to the PTO by e-mail.

Inquiries of a general nature should be directed to the Group 1800 receptionist at (703) 308-0196.


David L. Fitzgerald
Patent Examiner, Art Unit 1812
21 February 1995


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